Table 2. *Univariate analysis of outcomes*

	Early neurologic improvement*		Complete independence at day 90†		Any ICH		Symptomatic intracranial hemorrhage	
	Present (n = 60)	Absent (n = 67)	Present (n = 44)	Absent (n = 83)	Present (n = 61)	Absent (n = 66)	Present (n = 5)	Absent (n = 122)
Females	19 (32)	19 (28)	11 (25)	27 (33)	20 (33)	18 (27)	2 (40)	36 (30)
Age, years	72 ± 9	75 ± 9	71 ± 8	74 ± 10	72 ± 9	74 ± 10	78 ± 8	73 ± 10
Baseline NIHSS score	13 (5-30)	11 (4-24)‡	11 (4-30)	13 (4-26)‡	14 (4-24)	11 (4-30)‡	15 (12-21)	12 (4-30)
Onset to treatment time	127.5 (50-180)	140 (78-178)	133.5 (50-180)	139 (78-180)	139 (79-180)	133.5 (50-180)	120 (105-143)	136.5 (50-180)
Hypertension	36 (61)	44 (67)	27 (61)	53 (65)	38 (62)	42 (64)	4 (80)	76 (63)
Diabetes mellitus	7 (12)	17 (25)‡	6 (14)	18 (22)	14 (23)	10 (15)	0 (0)	24 (20)
Hyperlipidemia	16 (27)	18 (27)	11 (25)	23 (28)	13 (21)	21 (32)	0 (0)	34 (28)
Atrial fibrillation	26 (44)	32 (48)	16 (36)	42 (51)	30 (49)	28 (42)	4 (80)	54 (45)
Current smoking	10 (17)	21 (31)	9 (21)	22 (27)	16 (26)	15 (23)	1 (20)	30 (25)
Alcohol consumption	30 (51)	29 (43)	22 (51)	37 (45)	28 (46)	31 (47)	1 (20)	58 (48)
Cardioembolic (subtype)	37 (62)	35 (52)	23 (52)	49 (59)	38 (62)	34 (52)	5 (100)	67 (55)
CO group	8 (13)	19 (28)‡	3 (7)	24 (29)§	19 (31)	8 (12)§	1 (20)	26 (21)

Values are mean ± standard deviation in age, median (range) in baseline NIHSS score, and interval between onset and treatment time, or number (%).
*Reduction in NIHSS score of ≥4 points within the initial 24 hours.
†Defined as mRS score of 0 or 1. Eleven patients with a score of ≥2 before stroke onset were excluded.
‡$P < .05$.
§$P < .01$.

Table 3. *Multivariate analysis of outcomes*

	Absence of early neurologic improvement*			mRS score ≥2 at day 90			Any ICH		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
CO group	3.79	1.39-11.42	.008	4.44	1.38-19.96	.011	3.11	1.23-8.48	.016
Diabetes mellitus	2.77	1.03-8.15	.043	—	—	—	—	—	—
Baseline NIHSS score (per 1-point increase)	0.91	0.85-0.98	.011	1.05	0.98-1.13	.144	1.05	0.98-1.12	.165

Adjusted for age, sex, and confounders with an association of $P < .05$ with each outcome in univariate analysis.
Symptomatic intracranial hemorrhage was not tested due to the absence of significantly associated variables in univariate analysis.
*Increase, no change, or decrease in NIHSS score of <4 points within the initial 24 hours.

sonothrombolysis may improve the outcomes of patients with ICA occlusion, at which point this quick screening using US will work well.

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Effect of Prothrombin Complex Concentrate on Hematoma Enlargement and Clinical Outcome in Patients with Anticoagulant-Associated Intracerebral Hemorrhage

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Key Words
Intracerebral hemorrhage · Hematoma enlargement · Warfarin · Prothrombin complex concentrate

Abstract
Background: The present study was carried out to determine the effect of prothrombin complex concentrate (PCC) on hematoma enlargement (HE) and the early clinical outcome of intracerebral hemorrhage (ICH) patients on long-term warfarin treatment. ***Methods:*** The medical records and computed tomography (CT) images of 50 consecutive ICH patients on long-term warfarin treatment (35 men, 15 women; 69 ± 12 years old) were reviewed. International normalized ratio (INR) values, frequency of HE and clinical outcome were compared between patients treated with and without PCC. ***Results:*** INR values on admission were above 2.0 in 37 patients, of whom 19 were given PCC (PCC group) and 18 were not given PCC (control group). In these 37 patients, the frequency of HE ($p = 0.017$), the number of patients with a poor clinical outcome (modified Rankin Scale score ≥3 at 30 days or at discharge; $p = 0.045$) and in-hospital mortality ($p = 0.042$) were significantly higher in the control than in the PCC group. On multivariate logistic regression analysis with adjustment, PCC administration was independently associated (odds ratio 0.03, 95% confidence interval 0.00–0.63; $p = 0.023$) with a reduction in poor clinical outcome in ICH patients whose INR values were >2.0 on admission. ***Conclusions:*** Immediate INR reversal with PCC may prevent HE and subsequent poor outcome.

Introduction

Intracerebral hemorrhage (ICH) is a life-threatening complication of oral anticoagulation therapy. The relative risk of ICH during warfarin treatment is more than 10-fold in patients over 50 years of age [1]. Warfarin use increases not only the risk of ICH frequency but also the risk of hematoma enlargement (HE), thus worsening the severity of ICH and resulting in a poor outcome [2–8].

When serious ICH occurs in patients on warfarin treatment, immediate and complete reversal of coagulopathy is important. In order to reverse the effect of warfarin, vitamin K, fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) is given in addition to reduction or discontinuation of warfarin, depending on the international normalized ratio (INR) value. It has been reported that PCC administration reverses the INR value

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faster than FFP or vitamin K [4, 9–13]. However, the effects of PCC administration on preventing HE and on clinical outcome have not yet been clearly demonstrated.

The aim of the present study was to examine the efficacy of PCC for ICH in patients on warfarin treatment with respect to HE.

Methods

We studied 50 patients on warfarin treatment who were admitted to our stroke care unit within 3 days after ICH onset from January 1999 to December 2003. Patients with ICH due to aneurysmal rupture, vascular malformations, hemorrhagic transformation after brain infarction or brain tumor, as well as those who hemorrhaged primarily into the ventricles, were excluded. There were 35 men and 15 women, and their median age was 72 years (range 16–89 years). Twenty-two patients were given PCC (PCC group) and the remaining 28 were not (control group).

Written informed consent was obtained from the patients or their family before PCC was given. We used a commercially available PCC (PPSB-HT Nichiyaku; Nihon Pharmaceutical, Tokyo, Japan) which contains 500 IU of factors II, VI, IX and X, as well as 380 U of protein C, in 25 ml. For each patient, the decision to administer PCC, as well as the decision regarding how much to administer, was made by the physicians in charge based on our previous studies [14–16]. The INR values of all patients were examined on admission, within 2 h after PCC administration and 24 h after.

The presence, location and volume of ICH were verified on CT scan immediately following admission. The second CT examination was routinely performed within 24 h after admission. Additional CT scans were performed if a patient deteriorated clinically. All CT scans were reviewed and evaluated by neuroradiologists and neurologists who were blinded to the patients' clinical status. The locations of the hematomas were classified as putaminal, thalamic, lobar, pontine, cerebellar or other locations.

To calculate the ICH volume, the 3 diameters were multiplied and then divided by 2 ($A \times B \times C/2$) [17–20], where the longest diameter (A) and the largest diameter (B) perpendicular to A were measured using the centimeter scale on CT films of the slices showing the largest ICH area. The height of the hematoma (C) was calculated by multiplying the number of slices involved by the slice thickness. Hemorrhage volume within the ventricular system was not assessed. Parenchymal hemorrhage was considered to have enlarged when the volume on the follow-up CT was 1.4 times greater than the volume on the admission CT [21].

Hematoma volume (HV) on admission, final HV, frequency of HE and other baseline characteristics, such as age, gender, smoking status (previous and current), alcohol consumption (≥2 drinks per day), hypertension, diabetes mellitus, hypercholesterolemia, heart disease (including arrhythmia), liver disease (cirrhosis, active hepatitis, alcoholic liver damage, fatty liver and others), previous symptomatic ischemic stroke and previous symptomatic ICH, were compared between the 2 groups. Vascular risk factors were identified as follows: a history of antihypertensive medication, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on admission for hypertension; fasting blood glucose ≥126 mg/dl, positive 75-gram oral glucose tolerance test result or a history of antidiabetic medication and insulin for diabetes mellitus, and serum total cholesterol ≥220 mg/dl or a history of antihypercholesterolemic medication for hypercholesterolemia.

Systolic blood pressure, diastolic blood pressure and blood glucose were also assessed. In the acute stage, all patients had their systolic and diastolic blood pressures measured every 6 h after admission.

The patients' neurological state was evaluated by neurologists. Neurological deficits on admission were evaluated using the National Institutes of Health Stroke Scale (NIHSS) score. The clinical outcome was assessed using the modified Rankin Scale (mRS) score (from 0 to 5) at 30 days or at discharge, whichever occurred sooner [22]. Death was assigned an mRS score of 6 [23]. Good and poor outcomes were defined as an mRS score of 0–2 and 3–6, respectively.

Continuous values are expressed as means ± SD or medians and range. The clinical characteristics of ICH patients given PCC were compared to those of the ICH patients not given PCC using the χ^2 test, the unpaired Student's t test and the Mann-Whitney U test, as appropriate. In patients with an INR >2.0, similar comparisons were made, as an INR >2.0 was found to be one of the predisposing factors for enlargement of ICH in patients treated with warfarin [14]. A p value less than 0.05 was considered significant. Then, the background characteristics of patients with a good outcome and those with a poor outcome were compared. To identify the independent predictors for poor outcome, a multivariate logistic regression analysis with adjustments for age and gender was conducted using the clinical characteristics that showed a significant ($p < 0.05$) or marginally significant ($0.05 \leq p < 0.1$) correlation with each indicator as independent variables on univariate analyses.

Results

The primary underlying diseases that required anticoagulation were nonvalvular atrial fibrillation in 27 patients, mitral or aortic valve replacement in 8, deep vein thrombosis in 4, dilated cardiomyopathy in 3, old myocardial infarction in 3, coronary artery bypass graft for ischemic heart disease in 2, complicated atheromatous lesions in the aortic arch in 2 and peripheral arterial disease in 1. Thirty-five patients had a past history of brain infarction.

PCC was given to reverse the INR in 22 of the 50 ICH patients a median of 7.0 h (range 1.0–71.5 h) after the onset of ICH. The PCC doses were 1,500 IU in 3 patients, 1,000 IU in 2 and 500 IU in 17. INR values on admission were not significantly different between the PCC and control groups ($p = 0.215$). No significant differences were found between the groups for most of the baseline characteristics, including the frequency of vitamin K or FFP administration and systolic and diastolic blood

pressures on admission and 6, 12 and 24 h after hospitalization (table 1).

HE tended to be more frequent in the control group than in the PCC group (43 vs. 18%; p = 0.076), although admission HV, final HV and other hematoma characteristics were not different between the groups (table 1). The frequency of poor outcome (71 vs. 45%; p = 0.063) and in-hospital mortality (25 vs. 5%; p = 0.064) tended to be higher in the control group than in the PCC group (table 1).

The admission INR value was >2.0 in 37 of the 50 ICH patients on warfarin treatment. Of these 37, 19 were given PCC, while the other 18 patients were not. Two patients were given 1,500 IU of PCC, 2 were given 1,000 IU and 15 were given 500 IU. INR values on admission, administration frequency of vitamin K and FFP, baseline clinical characteristics and hematoma characteristics were not significantly different between the 19 patients in the PCC group and the 18 in the control group with an admission INR >2.0 (table 2).

Though the difference in HE was not significant between the 2 groups when all 50 ICH patients on warfarin were included, HE was more common in the control group than in the PCC group (56 vs. 16%; p = 0.017) for subjects with an admission INR >2.0 (table 2; fig. 1).

The number of patients with a poor outcome (78 vs. 42%; p = 0.045) and the in-hospital mortality (33 vs. 5%, p = 0.042) were significantly higher in the control group than in the PCC group among the patients with an admission INR >2.0 (table 2).

INR values 2 h [median 1.17 (range 0.89–1.72) vs. 1.85 (1.27–4.00); p < 0.001] and 24 h [median 1.14 (range 0.89–1.48) vs. 1.52 (1.17–3.00); p < 0.001] after PCC administration were significantly lower in the PCC group than in the control group. Furthermore, similar results [2 h after: median 1.21 (range 0.89–1.72) vs. 2.09 (1.85–4.00), p < 0.001; 24 h after: median 1.14 (range 0.89–1.48) vs. 1.70 (1.17–3.00), p = 0.003] were seen among patients whose admission INR was >2.0 (table 3).

Of the 37 patients with an admission INR >2.0, 22 had a poor outcome at 30 days or at discharge, while 15 had a good outcome. With respect to the clinical characteristics of these 37 patients, diastolic blood pressure (89 ± 20 vs. 77 ± 17 mm Hg; p = 0.054) and NIHSS score [median 14 (range 1–42) vs. 7 (1–30); p = 0.085] on admission tended to be higher in patients with a poor outcome than in those with a good outcome (table 4).

With respect to hematoma characteristics, the final HV was larger in the 22 patients with a poor outcome than in the 15 with a good outcome (60.7 ± 92.3 vs. 11.2 ± 12.8 cm^3; p = 0.047; table 4). Admission HV tended to be larger (39.2 ± 65.3 vs. 9.5 ± 10.5 cm^3; p = 0.091) and thalamic hemorrhage tended to be more frequent (64 vs. 33%; p = 0.099) in patients with a poor outcome than in those with a good outcome (table 4).

PCC was given more frequently to patients with a good outcome than to patients with a poor outcome (73 vs. 36%; p = 0.045), though there was no significant difference in the administration frequencies of vitamin K (60

Table 1. Clinical characteristics of the PCC and control groups

	PCC group (n = 22)	Control group (n = 28)	p value
Baseline characteristics			
Age, years	69.7 ± 8.2	68.7 ± 13.9	0.773
Males	15 (68%)	20 (71%)	0.804
Smoking	11 (50%)	18 (64%)	0.310
Drinking	9 (41%)	10 (36%)	0.707
Hypertension	19 (86%)	23 (82%)	0.999
Diabetes mellitus	4 (18%)	6 (21%)	0.999
Hypercholesterolemia	10 (45%)	7 (25%)	0.130
Heart disease	15 (68%)	20 (71%)	0.804
Liver disease	1 (5%)	3 (11%)	0.621
Previous ischemic stroke	15 (68%)	20 (71%)	0.804
Previous ICH	5 (23%)	2 (7%)	0.217
SBP on admission, mm Hg	165 ± 27	166 ± 25	0.881
DBP on admission, mm Hg	82 ± 20	86 ± 17	0.466
INR on admission	2.29 (1.14–3.96)	2.24 (1.11–4.23)	0.215
INR >2.0 on admission	19 (86%)	18 (64%)	0.108
Blood glucose, mg/dl	136 ± 56	137 ± 57	0.957
NIHSS score on admission	11 (2–34)	7 (1–42)	0.293
Vitamin K administration	15 (68%)	14 (50%)	0.196
FFP administration	1 (5%)	5 (18%)	0.211
Characteristics of hematoma			
Admission HV, cm^3	15.6 ± 16.3	29.2 ± 59.1	0.301
Final HV, cm^3	20.3 ± 23.6	44.4 ± 84.3	0.200
HE	4 (18%)	12 (43%)	0.076
Putaminal hemorrhage	3 (14%)	8 (29%)	0.306
Thalamic hemorrhage	11 (50%)	15 (54%)	0.802
Lobar hemorrhage	4 (18%)	7 (25%)	0.734
Pontine hemorrhage	2 (9%)	1 (4%)	0.576
Cerebellar hemorrhage	2 (9%)	1 (4%)	0.576
mRS at 30 days or at discharge			
mRS ≥3	10 (45%)	20 (71%)	0.063
In-hospital mortality (mRS = 6)	1 (5%)	7 (25%)	0.064

Values are presented as numbers of patients (percentage), means ± SD or medians (range). SBP = Systolic blood pressure; DBP = diastolic blood pressure.

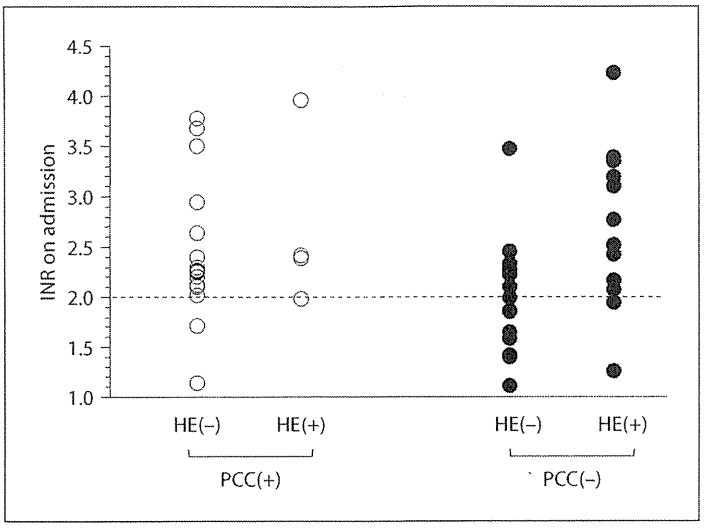

Fig. 1. HE according to INR value on admission shown on a scatter diagram. Though there was no significant difference in the frequency of HE between the PCC and the non-PCC groups for the whole group of 50 ICH patients on warfarin treatment, HE was more common in the non-PCC than in the PCC group (56 vs. 16%; p = 0.017) for subjects with an admission INR >2.0.

Table 2. Clinical characteristics of the PCC and control groups with INR >2.0 on admission

	PCC group (n = 19)	Control group (n = 18)	p value
Baseline characteristics			
Age, years	68.9 ± 8.5	66.7 ± 14.9	0.577
Males	12 (63%)	15 (83%)	0.269
INR on admission	2.39 (2.02–3.96)	2.44 (2.07–4.23)	0.867
NIHSS score on admission	10 (2–34)	6 (1–42)	0.209
Vitamin K administration	13 (68%)	10 (56%)	0.420
FFP administration	1 (5%)	3 (17%)	0.340
Characteristics of hematoma			
Admission HV, cm^3	16.1 ± 17.4	38.8 ± 72.3	0.193
Final HV, cm^3	21.6 ± 25.2	60.8 ± 102.1	0.114
HE	3 (16%)	10 (56%)	0.017
mRS at 30 days or at discharge			
mRS ≥3	8 (42%)	14 (78%)	0.045
In-hospital mortality (mRS = 6)	1 (5%)	6 (33%)	0.042

Values are presented as numbers of patients (percentage), means ± SD or medians (range).

vs. 63%; p = 0.823) and FFP (0 vs. 18%; p = 0.131) between the groups (table 4).

On multivariate logistic regression analysis using the significant ($p < 0.05$) and marginally significant ($0.05 \leq p < 0.1$) characteristics as independent variables with adjustments for age and gender, NIHSS score on admission (odds ratio 1.30, 95% confidence interval 1.01–1.69; p = 0.045 per 1-score increase) was independently related to poor outcome, and PCC administration (odds ratio 0.03, 95% confidence interval 0.00–0.63; p = 0.023) was independently associated with a reduction in poor outcome in the ICH patients with an admission INR >2.0 (table 5).

Table 3. Correction of INR value with PCC

	PCC group	Control group	p value
All patients			
INR on admission	2.29 (1.14–3.96)	2.24 (1.11–4.23)	0.215
INR after 2 h	1.17 (0.89–1.72)	1.85 (1.27–4.00)	<0.001
INR after 24 h	1.14 (0.89–1.48)	1.52 (1.17–3.00)	<0.001
Patients with INR >2.0			
INR on admission	2.39 (2.02–3.96)	2.44 (2.07–4.23)	0.867
INR after 2 h	1.21 (0.89–1.72)	2.09 (1.85–4.00)	<0.001
INR after 24 h	1.14 (0.89–1.48)	1.70 (1.17–3.00)	0.003

Values are presented as medians (range).

Discussion

In the present study investigating ICH in patients on warfarin treatment, the frequencies of HE, poor outcome and in-hospital mortality were significantly higher in the non-PCC (control) group than in the PCC group among patients with an admission INR >2.0. Moreover, PCC administration was one of the independent factors associated with a good clinical outcome in ICH patients on warfarin treatment.

Although there are no standard guidelines for reversing the anticoagulant effect in patients with ICH on warfarin, PCC appears to be a logical treatment for immediate reversal of the anticoagulant effect in such patients. The present study clearly demonstrated that HE occurred more frequently in ICH patients not treated with PCC than in those treated with PCC when the admission INR was >2.0. Flaherty et al. [24] reported that there was a trend toward a difference in HV according to INR levels in 51 ICH patients taking warfarin. Our previous report

Table 4. Characteristics of patients with mRS ≥3 or ≤2 (INR >2.0) at 30 days or at discharge

	mRS ≥3 (n = 22)	mRS ≤2 (n = 15)	p value
Baseline characteristics			
Age, years	67.1 ± 13.9	69.0 ± 8.6	0.639
Males	17 (77%)	10 (67%)	0.708
Smoking	14 (63%)	8 (53%)	0.531
Drinking	7 (32%)	8 (53%)	0.191
Hypertension	19 (86%)	11 (73%)	0.408
Diabetes mellitus	5 (23%)	3 (20%)	0.999
Hypercholesterolemia	8 (36%)	4 (27%)	0.724
Hypocholesterolemia	2 (9%)	1 (7%)	0.999
Heart disease	15 (68%)	12 (80%)	0.481
Liver disease	2 (9%)	2 (13%)	0.999
Previous ischemic stroke	17 (77%)	10 (67%)	0.708
Previous ICH	2 (9%)	4 (27%)	0.198
SBP on admission, mm Hg	171 ± 30	156 ± 22	0.111
DBP on admission, mm Hg	89 ± 20	77 ± 17	0.054
INR on admission	2.38 (2.07–4.23)	2.40 (2.02–3.78)	0.914
Blood glucose, mg/dl	154 ± 66	127 ± 53	0.212
NIHSS score on admission	14 (1–42)	7 (1–30)	0.085
Characteristics of hematoma			
Admission HV, cm^3	39.2 ± 65.3	9.5 ± 10.5	0.091
Final HV, cm^3	60.7 ± 92.3	11.2 ± 12.8	0.047
HE	10 (45%)	3 (20%)	0.166
Putaminal hemorrhage	7 (32%)	3 (20%)	0.481
Thalamic hemorrhage	14 (64%)	5 (33%)	0.099
Lobar hemorrhage	4 (18%)	3 (20%)	0.999
Pontine hemorrhage	1 (5%)	1 (7%)	0.999
Cerebellar hemorrhage	2 (9%)	1 (7%)	0.999
Reversal of anticoagulation			
Vitamin K administration	14 (63%)	9 (60%)	0.823
FFP administration	4 (18%)	0	0.131
PCC administration	8 (36%)	11 (73%)	0.045

Values are presented as numbers of patients (percentage), means ± SD or medians (range). SBP = Systolic blood pressure; DBP = diastolic blood pressure.

Table 5. Multivariate regression analysis for mRS ≥3 (INR >2.0)

Multivariate analysis	Odds ratio (95% CI)	p value
Age (per 1-year increase)	0.91 (0.80–1.03)	0.136
Gender (male)	4.12 (0.25–67.4)	0.321
DBP at admission (per 1-mm Hg increase)	1.01 (0.95–1.07)	0.687
NIHSS score on admission (per 1-point increase)	1.30 (1.01–1.69)	0.045
Final HV (per 1-cm^3 increase)	0.98 (0.94–1.03)	0.479
Thalamic hemorrhage	6.63 (0.69–64.2)	0.102
PCC administration	0.03 (0.00–0.63)	0.023

Multivariate logistic regression analysis was performed using the clinical characteristics that showed a significant ($p < 0.05$) or marginally significant ($0.05 \leq p < 0.1$) correlation with each indicator as independent variables on univariate analyses with adjustments for age and gender. CI = Confidence interval; DBP = diastolic blood pressure.

indicated that an INR value <2.0 on admission or for 24 h after immediate INR reversal with PCC prevented HE [14]. Therefore, it seems that immediate INR reversal is required to prevent HE in acute ICH patients with an INR >2.0.

Reversal of the effects of warfarin with PCC and vitamin K in patients with life-threatening neurological emergencies has been reported to be more rapid and effective than with FFP and vitamin K [9–12]. Siddiq et al. [13] reported that PCC in combination with FFP and vitamin K required less time for correction of warfarin-associated coagulopathy in neurosurgical emergencies than FFP and vitamin K alone.

Though PCC normalizes the INR more rapidly than FFP or vitamin K infusion, its effect on clinical outcomes has not yet been demonstrated. According to Boulis et al. [9], although the rate of correction was greater and the time to correction was shorter for PCC than for FFP, no difference in neurological outcomes was detected between patients treated with PCC and those treated with FFP. Although the present study did not include many data on FFP, it showed the effect of PCC administration not only on INR reversal but also on the subsequent outcome in patients whose INR value on admission was >2.0. Results such as the above were shown in the present study, but it may be necessary to perform randomized controlled trials with larger numbers of patients to more precisely evaluate the effect of PCC on outcome.

Kazui et al. [25] reported that HE was seen in 20% of intracranial hemorrhage patients not treated with antithrombotic agents, and enlargement of hematoma had stopped within 6 h after onset in 83% and within 24 h in 100%. Kawamata et al. [26] resumed anticoagulation in 12 patients with intracranial hemorrhage related to warfarin within 3 days and found no HE or rebleeding. Therefore, in order to avoid worsening hemorrhagic complications, an interval of 3 days wherein the INR is fully corrected with PCC may be required before resumption of anticoagulation.

Previous studies have shown that elevated blood pressure increases the risk of HE [25, 27]. Blood pressure control in the acute phase of hemorrhage in patients treated with warfarin appears to be as important as in those not treated with warfarin. In the present study, there was no significant difference with regard to 24-hour blood pressure control between the PCC group and the non-PCC group nor between the good outcome group (mRS score ≤ 2) and the poor outcome group (mRS score ≥ 3). Therefore, it seems that the effect of PCC found in the present study was not associated with blood pressure.

The present study has several limitations. Since the study was a nonrandomized, uncontrolled design, there might have been some selection bias. Furthermore, the patients received a variety of combination therapies. Administration criteria for PCC, vitamin K and FFP were not well defined, and the doses were not uniform. Prospective trials involving large populations of patients on warfarin are needed to overcome these limitations and clarify the remaining unresolved issues.

In conclusion, immediate INR reversal with PCC may prevent HE and subsequent poor outcome for ICH patients on warfarin treatment.

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Disclosure Statement

No conflicts of interest exists.

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High level of plasma adiponectin in acute stroke patients is associated with stroke mortality

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ABSTRACT

We examined the association between plasma adiponectin (ADPN) levels and cardiovascular mortality in acute stroke patients. We enrolled 552 consecutive acute stroke patients. Measurements were made at baseline and the patients were followed prospectively. The primary endpoint was cardiovascular (stroke or ischemic heart disease) death and the secondary endpoint was all-cause death. During the median follow-up period of 17 months, 39 patients died, 15 being due to stroke. No patients died of ischemic heart disease. After adjustment for age, sex, presence of hypertension, diabetes mellitus, and hyperlipidemia, the highest tertile of ADPN level (>11.7 μg/ml) was associated with stroke mortality (hazard ratio: 6.55, 95% confidence interval: 1.73–24.8), but not with all-cause mortality (hazard ratio: 1.89, 95% confidence interval: 0.95–3.77). High levels of plasma ADPN can be a predictor of stroke mortality during the 17 months following an episode of acute stroke in patients.

1. Introduction

Adiponectin (ADPN) is a peptide hormone secreted by adipocytes, shown to have a number of beneficial effects, such as anti-atherosclerosis and anti-inflammatory properties, and improvement of insulin resistance in the general population [1]. A number of reports suggested that hypoadiponectinemia is associated with high incidence of coronary artery disease [2] and of ischemic stroke [3]. Hypoadiponectinemia in patients with ischemic stroke was associated with long-term mortality [4]. In an animal model, ADPN exhibited vascular protection and prevention of brain damage after acute ischemic injuries, which were mediated by an endothelial nitric oxide synthase-dependent mechanism [5]. In these studies, it was suggested that a low level of ADPN is a cardiovascular risk factor and the secretion or action of ADPN might reduce the risk of cardiovascular disease (CVD).

On the contrary, several recent studies demonstrated that a high level of ADPN was associated with risk of CVD events and mortality in the general population [6], as well as in patients with chronic heart failure [7–9], coronary artery disease [10], or chronic kidney disease [11]. ADPN was shown to improve insulin resistance, and administration of ADPN decreased body weight in animal model [12]. It is suggested that high levels of ADPN might act to promote wasting and cause body weight loss, which is associated with poor prognosis in CVD patients.

Thus, it is unclear whether ADPN plays a beneficial or a harmful role in CVD. The purpose of the present study was to examine the association between plasma ADPN levels and cardiovascular mortality in acute stroke patients.

2. Methods

2.1. Subjects

This was a single-center hospital-based prospective study that was approved by the Institutional Research and Ethics Committee of the National Cardiovascular Center, Japan. We registered 569 patients who were admitted to our Stroke Care Unit within 7 days of stroke onset from April 1, 2005 to August 31, 2007. Not counted in this group were patients with subarachnoid hemorrhage due to a ruptured aneurysm and those with massive brain hemorrhage requiring neurosurgical treatment. Because informed consent was not obtained from 17 patients, 552 patients (men/women = 367/185, median age, 71 years) were actually enrolled in the present study.

2.2. Baseline assessment

Brain CT, carotid ultrasonography, and ECG were performed for all patients at the time of admission. The cervico-cephalic arteries of all patients with ischemic stroke, who did not have an implanted pacemaker, were evaluated with magnetic resonance angiography in addition to carotid ultrasonography. Two-dimensional echocardiography

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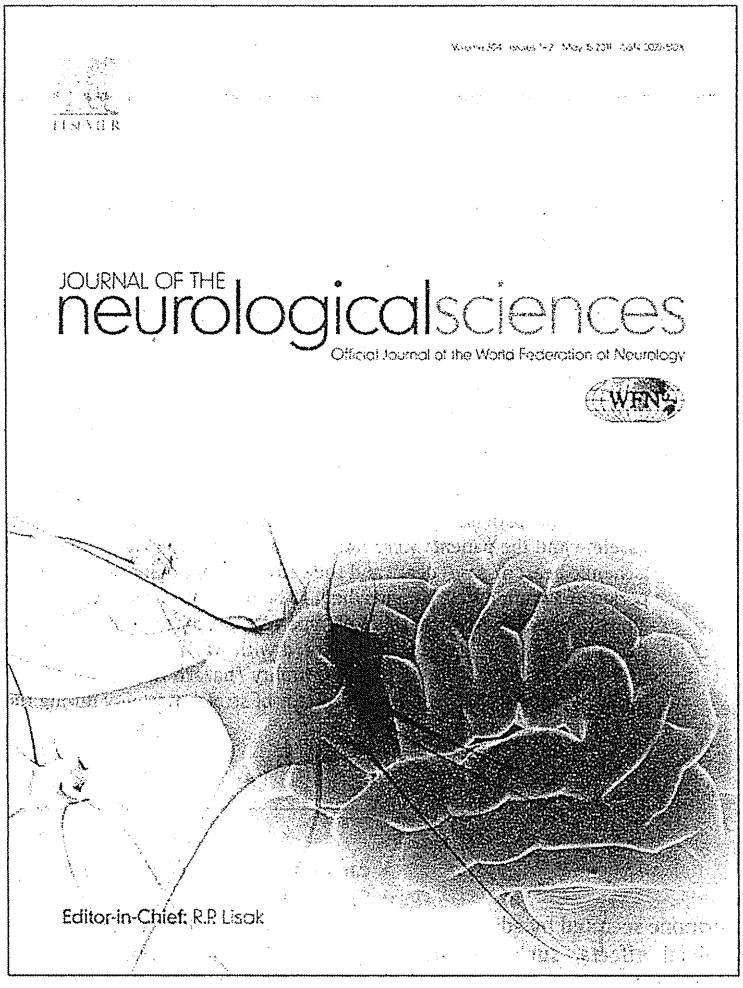

was done to investigate a potential embolic source in patients with ischemic stroke. Morning blood samples were collected after overnight fasting for measurement of glucose, lipid levels, and ADPN, 2 weeks after the stroke onset. For 91 patients in this study, we confirmed that there were no significant differences between serum ADPN levels on admission and 2 weeks after the stroke onset (data not shown). Plasma glucose was measured by the glucose-oxidase method and plasma ADPN level was measured by enzyme-linked immunosorbent assay. Triglycerides, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and creatinine were measured enzymatically. Renal function was assessed by the estimated glomerular filtration rate (eGFR) formula using the equations for the Japanese population [13] from serum creatinine: eGFR (ml/min/1.73 m^2) = $194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287} \times 0.739$ (for woman). Blood pressure was measured in all patients before discharge.

The diagnosis of stroke subtypes, such as atherothrombotic brain infarction (n = 90), lacunar infarction (n = 82), cardioembolic infarction (n = 130), other types of infarction (n = 123), and brain hemorrhage (n = 127), was made as previously described [14]. A diagnosis of atherothrombotic brain infarction was based on the presence of focal brain infarct(s) in the collection of evidence for occlusive lesions in the large cervical and intracranial arteries (either occlusion, ≥50% stenosis of the lumen diameter, or ulceration) determined by the clinical data. The diagnosis of lacunar infarction was made when a typical clinical syndrome was associated with a small infarct, <15 mm in diameter on CT, restricted to the territory of a perforating artery, and when no evidence of adjacent major artery occlusion or severe stenosis was found. Cardioembolic infarction was clinically diagnosed as described elsewhere [15]. If the patient had a combination of the above etiologies, or had undetermined etiologies (n = 72), if the stroke had other causes, such as arterial dissection, cerebral venous thrombosis (determined etiologies, n = 51), the index stroke was categorized to other types of infarction. The diagnosis of brain hemorrhage was based on CT findings.

National Institutes of Health Stroke Scale (NIHSS) scores were assessed on admission.

2.3. Patient follow-up

Patients were registered on the admission day. Information on vital status after the discharge from our hospital was obtained from medical charts of out-patient clinics or with telephone interview. All patients were followed up for at least 3 months until September, 2008. The primary endpoint was cardiovascular death (stroke and ischemic heart disease) and secondary endpoint was all-cause death.

2.4. Statistical analysis

Statistical analyses were performed using the SPSS 16.0J statistical package (SPSS, Inc., 2007). A value of $p<0.05$ was considered statistically significant.

ADPN levels were divided into tertiles (<6.8, 6.8–11.7, and >11.7 μg/ml). To determine the differences in clinical characteristics among the three groups of plasma ADPN levels or two groups of survivors and the dead, the χ^2 test, Student's t-test, Mann–Whitney U-test, ANOVA with Scheffe's F-test was used as appropriate. The correlations between plasma ADPN level and each cardiovascular risk factor were examined by a single regression analysis. Survival time was calculated from the date of admission to date of death. Survival rate was estimated by the Kaplan–Meier method and compared among the 3 groups by the log-rank test. The independent contribution of each factor to fatal events was estimated by the Cox proportional hazards models. Hazard ratios (HRs) for the incidence of fatal events were evaluated for to the highest tertile of ADPN level (>11.7 μg/ml) against the middle plus the lowest tertiles (≤11.7 μg/ml). Clinical covariates with the presence of hypertension, diabetes mellitus, and hyperlipidemia, were entered into the Cox proportional hazards models to adjust for potential confounders (Model 2). Subsequently, body mass index, eGFR, and NIHSS score on admission were added to covariates (Model 3).

3. Results

Median follow up period of this study was 17 months (range: 1–42 months). Plasma ADPN level of each stroke subtype were as follows: 9.3 ± 6.3 μg/ml in patients with atherothrombotic infarction, 9.0 ± 5.9 μg/ml in patients with lacunar infarction, 14.4 ± 11.1 μg/ml in patients with cardioembolic infarction, 10.5 ± 6.5 μg/ml in patients with other types of infarction, and 11.8 ± 8.6 μg/ml in patients with brain hemorrhage. Mean plasma ADPN level of patients with cerebral thrombosis (atherothrombotic infarction and lacunar infarction) was 9.2 ± 6.1 μg/ml, which was significantly lower than that in patients with cardioembolic infarction (14.4 ± 11.1 μg/ml, $p<0.001$).

Age, gender, body mass index, eGFR, frequencies of current smoker, diabetes, hyperlipidemia, median NIHSS score on admission, and the distribution of stroke subtypes were significantly different among the 3 levels of plasma ADPN (Table 1). In the lowest tertile, the larger number of younger patients and males was contained, and body mass index and eGFR were higher than those in the other tertiles. There were higher frequencies of current smokers, diabetes, and hyperlipidemia in the lowest tertile, and median NIHSS score on admission in the highest tertile was higher than those in the other 2 groups (Table 1). Plasma ADPN levels were significantly positively correlated with age ($r=0.360$, $p<0.001$), HDL cholesterol ($r=0.442$, $p<0.001$), and NIHSS score on admission ($r=0.161$, $p<0.001$), and were negatively correlated with body mass index ($r=-0.346$, $p<0.001$), triglycerides ($r=-0.307$, $p<0.001$), and eGFR ($r=-0.203$, $p<0.001$).

From a total of 552 patients, 4 patients dropped out during the follow up period; 1 patient with atherothrombotic brain infarction, 1 patient with lacunar infarction, and 2 patients with other types of infarction. From the remaining 548 patients, 39 patients died, of which 15 patients died of stroke (3 patients died during hospitalization) during the median follow-up period of 17 months. No patients died of ischemic heart disease. Other causes of death included heart

Table 1
Patient characteristics by tertiles of plasma ADPN.

Adiponectin level	Low (n = 184)	Middle (n = 183)	High (n = 181)	p
Age (years)	66 ± 11	71 ± 11	76 ± 10	<0.001
Male (n)	151	124	88	<0.001
Current smoker (n)	64	47	35	0.004
Ischemic heart disease (n)	21	16	25	0.311
Body mass index (kg/m^2)	24.5 ± 3.5	23.4 ± 3.4	21.2 ± 3.5	<0.001
Hypertension	150	140	148	0.366
Diabetes mellitus	60	55	36	0.016
Hyperlipidemia	77	62	52	0.030
Estimated GFR (ml/min/1.73 m^2)	76.2 ± 19.3	75.6 ± 22.8	65.7 ± 27.2	<0.001
Median NIHSS score on admission	5 (range: 0–28)	5 (range: 0–32)	8 (range: 0–36)	0.001
Stroke subtypes (n)				0.004
Atherothrombotic infarction	37	31	21	
Lacunar infarction	35	26	20	
Cardioembolic infarction	28	41	61	
Other types of infarction	43	43	35	
Brain hemorrhage	41	42	44	

Values are mean ± SD; GFR: glomerular filtration rate; NIHSS: National Institutes of Health Stroke scale.

failure (1 patient), cancer (3 patients) and pneumonia (5 patients). Table 2 shows a comparison of cardiovascular risk factors and stroke subtypes between the survivors and the fatal cases. The patients who died were significantly older ($p<0.001$), and had lower body mass index ($p=0.004$), lower diastolic blood pressure ($p=0.040$), lower eGFR ($p=0.021$), and higher plasma ADPN levels ($p<0.001$), higher NIHSS scores on admission ($p<0.001$). In comparison with the stroke subtypes, cardioembolic infarction contained the most fatal cases. There was no significant difference in ADPN levels between those with ischemic stroke and those with brain hemorrhage (11.2 ± 8.4 and 11.8 ± 8.6 μg/ml, respectively).

The survival rates were compared among 3 groups based on tertiles of plasma ADPN levels (Fig. 1). The highest level of ADPN was associated with poor outcome among the 3 groups in both the stroke ($p<0.001$) and all-cause mortalities patients ($p=0.001$).

The results of multivariate Cox regression analyses are shown in Tables 3a and 3b. The highest tertile of ADPN level was a significant predictor of stroke death after adjustment for age and sex (HR: 6.13, 95%CI: 1.61–23.3). Subsequently, with more adjustments for the presence of hypertension, diabetes mellitus, and hyperlipidemia in model 2, the highest tertile of ADPN remained a significant predictor of stroke mortality (HR: 6.55, 95%CI: 1.73–24.8). This association remained significant after additional adjustments for body mass index, eGFR, and NIHSS score on admission in model 3 (HR 4.69, 95% CI: 1.10–20.1). There was no significant interaction between ADPN level and variables for which distribution was different among tertiles of ADPN levels (data not shown). However, the highest tertile of ADPN level was not associated with all-cause mortality.

We analyzed for patients with ischemic stroke ($n=421$) as the same manner as analysis for all patients. The highest tertile of ADPN level was associated with stroke mortality (hazard ratio: 6.90, 95% CI: 1.34–35.5), but not with all-cause mortality (hazard ratio: 1.90, 95% confidence interval: 0.87–4.14) after adjustment for age and sex.

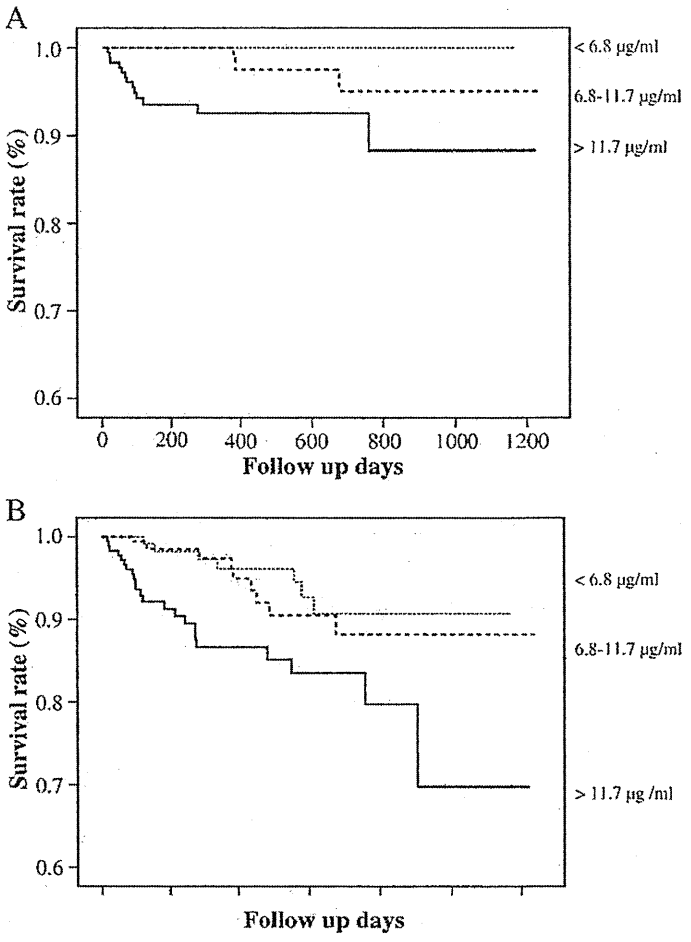

Fig. 1. Kaplan–Meier survival curves according to tertiles of plasma adiponectin concentration for (A) stroke mortality, and (B) all-cause mortality.

Table 2
Comparison of clinical parameters between survivors and fatal cases.

	Survivors (n=509)	Fatalities (n=39)	p
Age (years)	70±11	80±9	<0.001
Male (n)	341	22	0.218
Current smoker (n)	141	5	0.058
Ischemic heart disease (n)	60	2	0.295
Body mass index (kg/m^2)	23.2±3.7	21.4±3.5	0.004
Systolic blood pressure (mm Hg)	134±15	134±15	0.833
Diastolic blood pressure (mm Hg)	72±10	69±9	0.040
Total cholesterol (mg/dl)	170±37	167±36	0.603
Triglycerides (mg/dl)	113±50	102±43	0.167
LDL cholesterol (mg/dl)	108±32	107±37	0.849
HDL cholesterol (mg/dl)	42±12	41±13	0.666
Fasting plasma glucose (mg/dl)	107±35	105±27	0.800
Adiponectin (μg/ml)	10.9±8.1	16.5±10.2	<0.001
Estimated GFR, ml/min/1.73 m^2	73.1±23.5	63.9±26.8	0.021
Median NIHSS score on admission	5 (range: 0–32)	17 (range: 2–36)	<0.001
Stroke subtypes (n)			
Atherothrombotic infarction	85	4	
Lacunar infarction	81	0	
Cardioembolic infarction	111	19	
Other types of infarction			
Undetermined etiology	65	5	
Determined etiology	48	3	
Brain hemorrhage	119	8	

Values are mean±SD; LDL: low-density lipoprotein; HDL: high-density lipoprotein; GFR: glomerular filtration rate; NIHSS: National Institutes of Health Stroke scale.

4. Discussion

This is the first study demonstrating that a high level of plasma ADPN in acute stroke patients was strongly associated with a high risk of stroke death during the median follow-up period of 17 months.

Plasma ADPN levels might change by the influences of stroke severity and stroke subtypes. In this study, there was a significant positive correlation between ADPN levels and NIHSS scores on admission ($r=0.161$, $p<0.001$). Besides, ADPN knock-out mice were shown to exhibit increased cerebral infarction size [5]. Plasma ADPN levels were different in each stroke subtype in this study, consistent with a past study [16]: patients with atherothronbotic brain infarction and lacunar infarction had lower plasma ADPN levels and those with cardioembolic brain infarction had the highest.

ADPN was reported to increase energy expenditure through a direct action in the central nervous system in mice [17]. An increased level of plasma ADPN was observed in patients with heart failure with cachexia [18]. The authors suggested that the increased ADPN, which might occur in an attempt to normalize fatty acid metabolism, would cause body weight loss in patients with advanced heart failure. Recently, high levels of ADPN in patients with CVD were reported to be associated with the increased risk of mortality in both men and women [19,20]. In patients with coronary artery disease, high levels of ADPN turned out to be a risk factor for future CVD events or death [10,21,22], although another report showed no association between high levels of ADPN and CVD death [23]. Marousi S, et al. [24] reported that ADPN was significantly suppressed already by the early phases of ischemic stroke, and remained unchanged 6 months later. Prognostic implications in levels of ADPN have not been clarified. And they

Table 3a
Results of multivariate Cox regression analysis for the incidence of fatal events considering the highest tertile of adiponectin concentration against the middle plus the lowest tertiles.

	Hazard ratio (95% CI)	p
Stroke mortality		
Model 1	6.13 (1.61–23.3)	0.008
Model 2	6.55 (1.73–24.8)	0.006
Model 3	4.69 (1.10–20.1)	0.037
All-cause mortality		
Model 1	1.75 (0.88–3.48)	0.112
Model 2	1.89 (0.95–3.77)	0.070
Model 3	1.19 (0.54–2.62)	0.675

CI: confidence interval.
Model 1: adjusted for age and sex. Model 2 includes the covariates in model 1 plus the presence of hypertension, diabetes mellitus, and hyperlipidemia. Model 3 includes the covariates in model 2 plus body mass index, NIHSS score on admission, and estimated glomerular filtration rate.

recently reported that ADPN was not found to be associated with mortality after the ischemic stroke [25]. But their sample size is very small (n = 82), and follow up period is too short (6 months).

Another possible reason of high mortality in patients with high levels of ADPN could be the low clearance of ADPN attributable to the renal dysfunction. The kidneys are the main elimination apparatus for circulating ADPN [26,27]. Mild renal dysfunction as well as chronic kidney disease was a strong predictor of mortality and poor outcome in both patients with myocardial infarction [28] and stroke [29]. In the present study, eGFR was lower and ADPN was higher in the fatal cases than in the survivors. Relative to this observation, a high level of ADPN was demonstrated to associate with high mortality in patients with chronic kidney disease [11].

The present study was observational, and can only demonstrate associations. We speculate that ADPN plays a protective role in vascular injuries through exerting anti-atherosclerosis or anti-inflammatory effects; however, in high risk patients, such as CVD patients, ADPN level were raised to compensate for vascular injuries, which could result in harmful effects, notably, body weight loss and sarcopenia.

The limitations of this study are that the present investigation was conducted at a single-center with a prospective design. The sample size as well as the follow-up period might not be large enough to have a sufficient statistical power. However we demonstrated a strong association between high ADPN levels and increased risk of stroke mortality. Another limitation is that we measured total ADPN in the present study. It is known that ADPN consists of isoforms with various molecular weights (low-molecular weight; LMW, medium molecular weight; MMW, and high-molecular weight; HMW). These isoforms have different binding affinities for the ADPN receptors, and may have different bioactivities. Recently, a number of reports showed that HMW form of ADPN has more biological activity than LMW or MMW ADPN [30,31]. HMW ADPN, especially the HMW to total ADPN ratio, was significantly lower in patients with coronary artery disease than those without coronary artery disease in patients with type 2 diabetes [31]. Further analysis of ADPN isoforms with respect to cerebrovascular risk factors might clarify the contribution of ADPN to the pathogenesis of cerebrovascular disease.

Table 3b
Hazard ratio of each variable in Cox regression analysis (Model 3).

	Stroke death		All-cause death	
	Hazard ratio	p	Hazard ratio	p
Adiponectin level	4.69 (1.10–20.1)	0.037	1.19 (0.54–2.62)	0.675
Age	1.06 (0.99–1.13)	0.124	1.07 (1.03–1.11)	0.001
Sex	1.38 (0.46–4.16)	0.569	1.07 (0.53–2.16)	0.847
Hypertension	1.81 (0.39–8.32)	0.447	1.82 (0.74–4.46)	0.190
Diabetes mellitus	3.73 (1.10–12.7)	0.035	1.72 (0.78–3.80)	0.183
Hyperlipidemia	0.43 (0.11–1.67)	0.221	0.41 (0.18–0.93)	0.032
Body mass index	0.88 (0.74–1.06)	0.177	0.94 (0.84–1.05)	0.247
NIHSS score on admission	1.08 (1.01–1.16)	0.024	1.11 (1.07–1.16)	<0.001
Estimated GFR	1.01 (0.99–1.03)	0.377	1.00 (0.98–1.01)	0.537

NIHSS: National Institutes of Health Stroke scale; GFR: glomerular filtration rate.

In conclusion, a high level of ADPN in acute stroke patients was associated with an increased risk of stroke death during the 17 months of median follow up period after stroke. Further experimental and epidemiological studies are needed to elucidate possible roles of ADPN in cerebrovascular diseases.

Acknowledgments

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Clinical Characteristics by Topographical Distribution of Brain Microbleeds, With a Particular Emphasis on Diffuse Microbleeds

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From the perspective of the underlying pathogenesis of primary intracerebral hemorrhage (pICH), the topographical distribution of brain microbleeds (MBs) is divided into the lobar area and the deep brain or infratentorial areas. We investigated clinical features, including ambulatory blood pressure (ABP), of patients with MBs distributed in both areas (diffuse MBs). A total of 124 patients with first-ever acute stroke were enrolled prospectively. Gradient-echo T2*-weighted magnetic resonance imaging (MRI) was performed using a 1.5-T scanner. Patients were classified into 4 groups: MBs-negative group (n = 68), those with MBs in lobar areas (lobar group; n = 6), those with MBs in deep or infratentorial areas (deep or infratentorial group; n = 31), and those with MBs in both areas (diffuse group; n = 19). The admission casual BP (CBP) was recorded in all patients, and ABP was measured in the ischemic stroke patients. There were significant differences in the distribution of MBs ($P = .004$) among the 6 stroke subtypes. All stroke subtypes except transient ischemic attack had diffuse MBs; pICH had the highest prevalence of it (35%). The severity of white matter hyperintensity (WMH) differed among the 4 groups ($P < .0001$), with the diffuse group having the highest prevalence of early confluent (47%) and confluent types (21%). ABP and CBP were significantly higher in the deep and diffuse groups compared with the MBs-negative group, but did not differ between the lobar group and the MBs-negative group. Our data suggest that diffuse MBs are associated with hypertensive stroke, elevated BP, and severe WMH. The pathogenesis of diffuse MBs may be related to the more severe microangiopathy involved in hypertensive arteriopathy and cerebral amyloid angiopathy. **Key Words:** Magnetic resonance imaging—blood pressure—cerebral amyloid angiopathy—intracerebral hemorrhage—small-vessel disease.

Gradient-echo T2*-weighted magnetic resonance imaging (GE-MRI) sensitively detects the paramagnetic effect of blood breakdown products and can visualize brain microbleeds (MBs).[1] There is some pathological evidence suggesting that MBs observed on GE-MRIs are hemosiderin deposits.[1,2] On conventional GE-MRI, the prevalence of MBs has been reported to range from 4.5% to 6.8% in healthy elderly individuals,[3-6] from 54% to 71% in

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Y.Y., C.Y., and N.Y. analyzed and interpreted data; Y.Y., C.Y., Y.K., and K.M. wrote the manuscript; and all of the authors reviewed and approved the final version of the manuscript.

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patients with primary intracerebral hemorrhage (pICH),[2,4,7-9] and from 20% to 36% in patients with ischemic stroke.[10-12]

The prevalence of MBs generally is considered to be clinically correlated with aging, male sex, chronic hypertension, stroke subtype, and white matter hyperintensity (WMH).[3,5,8,13,14] Although the exact etiology of MBs is unclear, both hypertensive arteriopathy and cerebral amyloid angiopathy (CAA) are believed to be underlying pathogeneses of MBs.[1,2] MBs appear to be regionally associated with pICH.[15-17] Typically, pICH restricted to a lobar location results from CAA. This is in contrast to pICHs in the deep area (eg basal ganglia, thalamus) or infratentorial region, which are attributed mainly to hypertension. If this parallel between pICH and MBs were true, then established factors correlated with MBs would differ according to their topographical distributions.[14] Some previous studies have examined the association between the topographical distribution of MBs and clinical features.[7,14,18] In these studies, MB locations were divided mainly into the lobar area and the deep or infratentorial areas. Clinical features of MBs located in both areas, so-called "diffuse MBs," have not yet been clarified.

The present study investigated the relationship between the topographical distributions of MBs, particularly diffuse MBs, and clinical characteristics, especially blood pressure (BP; including ambulatory BP [ABP]), stroke subtypes, and white matter hyperintensity (WMH), in survivors with first-ever stroke.

Patients and Methods

Patient Selection

A total of 157 consecutive patients with first-ever stroke (excluding subarachnoid hemorrhage) who were admitted to our stroke care unit within 7 days of stroke onset between April 1, 2003, and March 31, 2004 were considered potential subjects for this study. Exclusion criteria were inability to undergo cerebral MRI, history of neurologic disorders or brain injuries, a neurosurgical operation or a recurrence within 7 days after stroke onset, death before informed consent could be obtained, and stroke as a result of catheterization. All protocols were approved by the institutional review board on March 17, 2003 (approval 14-41).

Of the initial 157 potential subjects, 6 individuals refused to be enrolled, 3 had a contraindication for MRI scanning, 8 had undergone a neurosurgical operation shortly after stroke onset, 2 had recurrent stroke, 7 died within 7 days after onset, and 5 had a stroke as a result of catheterization. Of the remaining 126 subjects, 2 subjects had motion artifacts on MRI. Consequently, a total of 124 subjects (78 men, 46 women; age range, 33-85 years) were studied prospectively. No subject was receiving thrombolytic therapy.

Baseline Assessment

Clinical characteristics, including age, sex, history of ischemic heart disease, smoking status, and presence of hypertension, diabetes mellitus, hyperlipidemia, and atrial fibrillation (AF), were recorded. Hypertension was defined as systolic BP (SBP) >140 mm Hg and/or diastolic BP (DBP) >90 mm Hg on repeat measurements at intervals of 1 week, or the use of antihypertensive medication. Diabetes mellitus was defined as fasting serum glucose level ≥126 mg/dL or the use of antidiabetic medication. Hyperlipidemia was defined as fasting serum total cholesterol level ≥220 mg/dL and/or fasting serum triglyceride level ≥200 mg/dL and/or the use of an antihyperlipidemic agent. Patients who were current smokers at the time of their index stroke were considered current smokers. AF was diagnosed on electrocardiography. A history of previous ischemic heart disease or recent treatment with an antithrombotic agent, such as an antiplatelet or anticoagulant agent, was obtained from the hospital records or the patients themselves.

Diagnosis of Stroke Subtypes

The diagnosis of stroke subtype, including pICH, atherothrombotic brain infarction (ATBI), lacunar infarction (LI), cardioembolic infarction (CEI), other types of infarction (OTI), and transient ischemic attack (TIA), was made according to the criteria of the Classification of Cerebrovascular Diseases III.[19] Diagnoses were done as described previously,[20,21] using MRI, MR angiography, conventional cerebral angiography, carotid ultrasonography, or transesophageal echocardiography, as appropriate. A diagnosis of ATBI was based on the presence of focal brain infarct(s) as evidence of occlusive lesions in the large cervical and intracranial arteries (occlusion, ≥50% stenosis of the lumen diameter, or ulceration). The diagnosis of LI was made when a typical clinical syndrome was associated with a small infarct (<15 mm in diameter) restricted to the territory of a perforating artery, and when no evidence of adjacent major artery occlusion or severe stenosis was found. CEI was clinically diagnosed as described elsewhere.[20] In patients with a combination of the foregoing etiologies, a stroke with another cause (eg, arterial dissection, cerebral venous thrombosis), or an undetermined etiology, the index stroke was categorized as OTI. pICH was defined as spontaneous nontraumatic intracerebral bleeding with no evidence of any vascular malformation or brain tumor as the source of the hematoma. TIA was defined as a sudden, focal neurologic deficit consistent with a vascular origin lasting less than 24 hours; episodes of isolated vertigo, migraine equivalents, transient global amnesia, and nonfocal symptoms were specifically excluded.

MRI Images

MRI was performed using a 1.5-T scanner (Magnetom Vision; Siemens, Erlangen, Germany). On the 11th

hospital day on average, GE-MRI was performed in the axial plane with the following parameters: repetition time (TR), 736 ms; echo time (TE), 20 ms; flip angle (FA), 30°; section thickness, 4 mm; gap width, 2 mm; matrix, 192 × 256; field of vision, 172 × 230 mm^2. Axial fast spin-echo T2-weighted images (TR, 5400 ms; TE, 99 ms) also were obtained with the same section thickness and matrix.

MBs were defined on GE-MRI as rounded areas of signal loss, 2-5 mm in diameter; they were not the lesion(s) responsible for the index stroke. Two investigators (C.Y. and N.Y.), who were blinded to the patients' data, reviewed the number and location of the MBs in the entire brain. Symmetric hypointensities in the globus pallidus (most likely representing calcification) and flow void artifacts of pial vessels were excluded.

The MBs-positive group was divided into 3 subgroups (lobar, deep or infratentorial, and diffuse groups) based on the topographical distribution of the MBs (Fig 1). The lobar group and the deep or infratentorial group were categorized according to a previous report[14] as follows. The lobar group included MBs located in the cerebral cortices, the subcortical white matter, or periventricular white matter. The deep or infratentorial group included MBs located in the basal ganglia; thalamus; white matter of the corpus callosum, internal, external, and extreme capsules; and infratentorial (brain stem and cerebellum). The diffuse group included MBs located in both the lobar and the deep or infratentorial areas. No effort was made to define lesions as being either purely cortical or subcortical white matter, which is not considered possible on image analysis. WMHs also were classified into 4 subgroups (absent, punctate, early confluent, and confluent) based on T2-weighted imaging.[22]

BP Measurement

In all patients, casual BP (CBP) was measured on admission with the patient in the decubitus position using a standard mercury sphygmomanometer before administration of any drugs. ABP was measured in all patients with ischemic stroke or TIA, but not in those with pICH, in whom antihypertensive therapy was often started soon after admission. To eliminate the expected transient BP elevation during the initial week after ischemic stroke, ABP monitoring (ABPM) was done just before discharge. ABP was measured every 30 minutes during the day (6:01 AM to 10:00 PM) and every 60 minutes during the night (10:01 PM to 6:00 AM) with a portable automatic BP monitoring device (model TM2425; A&D Co Ltd, Tokyo, Japan). In the majority of patients, the ABP values obtained by the Korotkoff method were used for analysis. When data were not obtained by the Korotkoff method, data obtained by the oscillometric method were used for the analysis. Three patients with ischemic stroke or TIA did not have ABPM; 2 of the patients refused ABPM, and 1 patient was at risk for subcutaneous ecchymoma. Two patients in whom BP readings could not be achieved >75% of the time were excluded from the ABP analysis. Based on previous studies demonstrating similar applicability of 24-hour ABPM in AF as in sinus rhythm,[23,24] patients with AF also underwent ABPM in this study. Thus, ABPM was successfully completed in 85 patients with ischemic stroke or TIA (during the 21st hospital day on average). Before ABPM, 21 patients (24.7%) had been started on antihypertensive therapy by the attending physician because of previous coronary disease, chronic heart failure, or significantly elevated BP.

The 24-hour average BP (24-hour SBP and 24-hour DBP), the mean values of daytime BP (day SBP and day

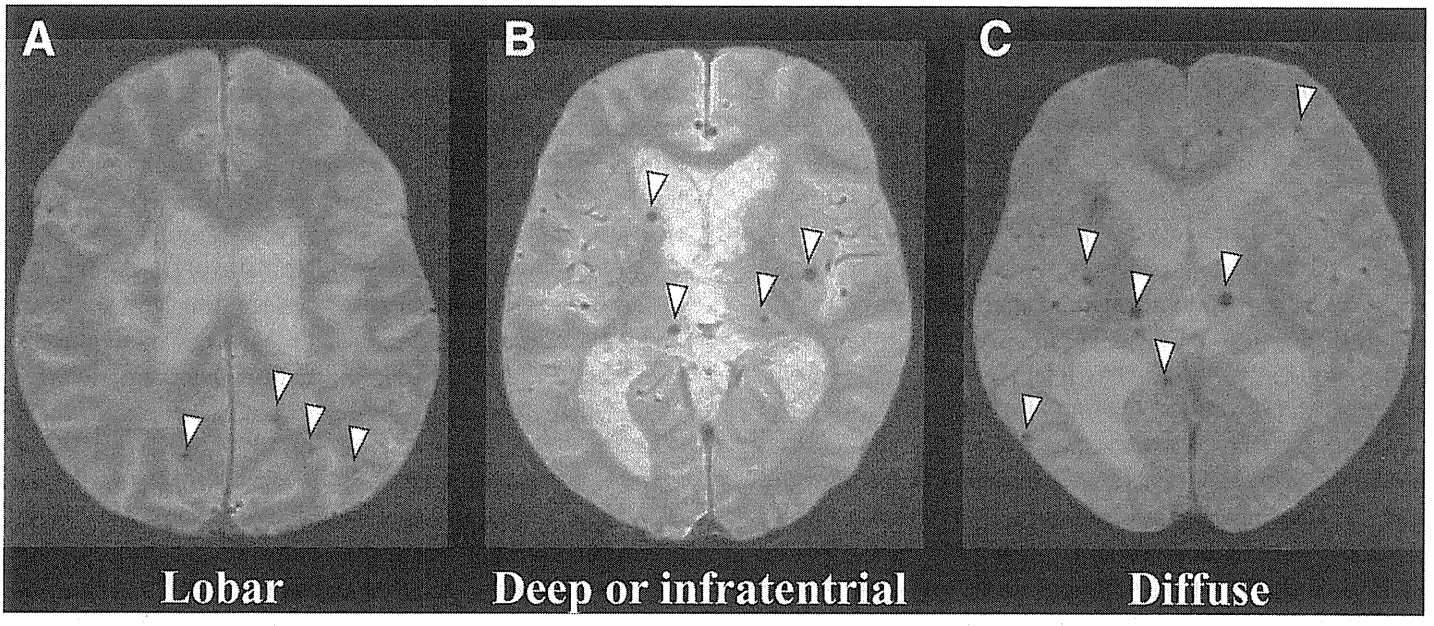

Figure 1. *Representative images of each group classified by the topographical distribution of MBs. Gradient-echo T2*-weighted MRI images show representative images of patients with MBs in lobar areas (A, lobar group), those with MBs in deep or infratentorial areas (B, deep or infratentorial group), and those with MBs in both areas (C, diffuse group). MBs were defined as rounded areas of signal loss (arrowheads).*

DBP), and the mean values of nighttime BP (night SBP and night DBP) were calculated. The degree of the nocturnal BP dip was calculated as follows: (day SBP − night SBP)/day SBP × 100. Nondippers were defined as patients without a nocturnal SBP dip (>5%), as described previously.[25]

Statistics

Statistical analyses were performed using SPSS version 11.0 (SPSS Inc, Chicago, IL). To compare the number and distribution of MBs among stroke subtypes, the χ^2 test or Kruskal-Wallis test was used, as appropriate. To compare clinical characteristics and the BP data between the MBs-negative and MBs-positive groups, the χ^2 test or Student's t test was used. Clinical variables with statistical significance in comparisons between 2 groups also were compared among the 4 groups, using the χ^2 test or one-way analysis of variance with Dunnett's q test. Statistical significance was set at $P < .05$.

Results

In all, 296 MBs (mean, 2.4 per patient; range, 0-28) were identified. The prevalence of a single MB was 15% (18/124), and that of 2 or more MBs was 31% (38/124). Eighty MBs were located in lobar areas, and 216 were located in deep or infratentorial areas (55 in the basal ganglia, 79 in the thalamus, 33 in the deep white matter, 32 in the brain stem, and 17 in the cerebellum). In terms of topographical distribution, 65 patients (55%) were MBs-negative, 6 patients (5%) were in the lobar group, 31 patients (25%) were in the deep or infratentorial group, and 19 patients (15%) were in the diffuse group.

Among stroke subtypes, the number (median/mean ± standard deviation) of MBs was the highest in pICH (3/4.4 ± 5.4; $P < .0001$, Kruskal-Wallis test), followed by LI (0/2.8 ± 6.3), OTI (0/2.2 ± 4.6), ATBI (0/1.4 ± 2.1), CEI (0/1.3 ± 4.6), and TIA (0/0.1 ± 0.3). There were significant differences in the prevalence of MBs among the stroke subtypes ($P < .0001$; Fig 2). The prevalence of MBs was the highest in pICH (n = 27/34; 79%), followed by ATBI (n = 6/13; 46%), OTI (n = 5/13; 39%), LI (n = 8/22; 36%), CEI (n = 9/30; 30%), and TIA (n = 1/12; 8%). Of the 27 pICH patients with MBs, 2 were in the lobar group, 13 were in the deep or infratentorial group, and 12 were in the diffuse group. Both pICH patients in the lobar group had a single lobar hemorrhage (CBP of the 2 patients was 164/72 mm Hg and 130/85 mm Hg), and had a history of hypertension; the patients in the 3 other groups had deep hemorrhages. There were also differences in the distribution of MBs among stroke subtypes ($P = .004$; Fig 2). Whereas lobar group patients were seen in the pICH, OTI, LI, and CEI stroke subtypes (3.3%-9.1%), they were not seen in the ATBI and TIA stroke subtypes. The diffuse group was present in all stroke subtypes except TIA. The proportion of the diffuse group was the highest in pICH

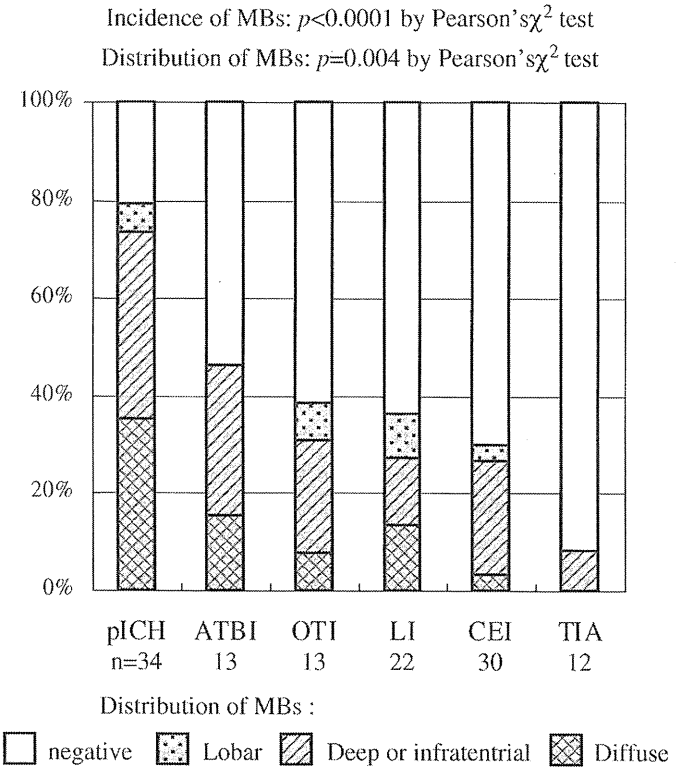

Figure 2. *Comparison of the incidence and distribution of MBs by stroke subtype. The incidence of MBs differs significantly among stroke subtypes (P < .0001), as does the distribution of MBs (P = .004).*

(n = 12/34; 35%) followed by ATBI (n = 2/13; 15%), LI (n = 3/22; 14%), OTI (n = 1/13; 8%), CEI (n = 1/30; 3%), and TIA (n = 0/12; 0%).

Table 1 compares clinical characteristics and BP components of the MBs-negative and MBs-positive groups. Fifty-six patients had MBs (45%). Hypertension (96%; $P = .008$) was more frequent in the MBs-positive group than in the MBs-negative group. The prevalence of AF was lower in the MBs-positive group (14%) than in the MBs-negative group (29%; $P = .045$). There were significant differences in the severity of WMH between the 2 groups ($P = .001$); severe WMH (eg, early confluent, confluent) was more frequent in the MBs-positive group than in the MBs-negative group. CBP and ABP values were significantly higher in the MBs-positive group. There was no difference in the frequency of nondippers between the 2 groups.

Clinical variables that were statistically significantly different in the comparison between the MBs-positive and MBs-negative groups (ie, prevalences of hypertension and AF, and differences in the severity of WMH) were further compared among the 4 MB topographical distribution subgroups (Table 2). The severity of WMH remained significant ($P < .001$); the diffuse group had the highest prevalence of early confluent (n = 9/19; 47%) and confluent types (n = 4/19; 21%).

Table 3 compares the BP values in the 4 MB topographical distribution groups. On admission, SBP and DBP were similar in the lobar group and the MBs-negative group; but significantly higher in the deep (SBP,

Table 1. *Clinical characteristics and BP components of the MBs-negative and MBs-positive groups*

Clinical variable	MBs-negative (n = 68; 55%)	MBs-positive (n = 56; 45%)	*P*
Age, years, mean (SD)	69 (12)	67 (13)	.322
Male, n (%)	41 (60)	37 (66)	.507
Hypertension, n (%)	55 (81)	54 (96)	.008
Smoking, n (%)	33 (49)	23 (41)	.406
Hyperlipidemia, n (%)	30 (44)	22 (39)	.587
Diabetes, n (%)	26 (38)	17 (30)	.359
AF, n (%)	20 (29)	8 (14)	.045
Ischemic heart disease, n (%)	8 (12)	5 (9)	.608
WMH, n (%)			
Punctate	34 (50)	28 (50)	.001
Early confluent	7 (10)	11 (20)	
Confluent	1 (2)	9 (16)	
Antithrombotics, n (%)	16 (25)	6 (11)	.053
Casual BP			
SBP, mm Hg (SD)	160.6 (24.6)	179.4 (31.0)	<.0001
DBP, mm Hg (SD)	84.2 (13.9)	97.4 (15.6)	<.0001
Ambulatory BP*			
24-hour SBP, mm Hg (SD)	133.2 (20.0)	148.4 (15.6)	.001
Day SBP, mm Hg (SD)	134.5 (20.2)	150.5 (15.9)	.001
Night SBP, mm Hg (SD)	128.1 (21.7)	139.6 (17.4)	.018
24-hour DBP, mm Hg (SD)	75.6 (9.0)	84.9 (12.0)	<.0001
Day DBP, mm Hg (SD)	75.6 (9.0)	84.9 (12.0)	<.0001
Night DBP, mm Hg (SD)	71.4 (9.4)	80.5 (13.0)	<.0001
Nondipper, n (%)	32 (55.2)	10 (37.0)	.119

Continuous variables are presented as mean (SD) and compared with the Student *t* test. Pearson's χ^2 test was used for frequency comparisons.
*Evaluated in 85 patients with ischemic stroke (including TIA).

P = .007; DBP, *P* = .001) and diffuse (SBP, *P* = .002; DBP, *P* < .0001) groups compared with the MBs-negative group. All ABPs in the lobar group were similar to those in the MBs-negative group, whereas all ABPs except night SBP were significantly higher in the deep group (24-hour SBP, *P* = .01; day SBP, *P* = .011; night SBP, *P* = .053; 24-hour DBP, *P* = .003; day DBP, *P* = .003; night DBP, *P* = .004) and diffuse group (24-hour SBP, *P* = .023; day SBP, *P* = .012; night SBP, *P* = .133; 24-hour DBP, *P* = .006; day DBP, *P* = .007; night DBP, *P* = .013) compared with the MBs-negative group. No significant difference in the frequency of nondippers was seen among the groups (Table 3).

Discussion

The hallmark of the present study is its classification of the topographical distribution of MBs. From the perspective of underlying pICH pathogenesis, such as CAA or hypertension, the generally accepted approach is to divide the topographical distribution of MBs into lobar and deep or infratentorial areas.[14,18] But MBs located in both areas (so-called "diffuse MBs") are often seen in daily clinical practice (a prevalence of 15% in the present study). Thus, it would seem practical to divide the MBs-positive group into 3 subgroups (lobar, deep or infratentorial, and diffuse) however, no previous study has used such a MBs classification scheme. This is the first study to investigate the relationship between clinical characteristics and the topographical distribution of MBs classified according to 4 types (including diffuse MBs).

There were significant differences in the prevalence of MBs among the stroke subtypes. Such differences might be linked to the very high prevalence of MBs in patients with pICH and the very low prevalence in patients with TIA, which were consistent with previous studies.[8,13] There also were differences in the distribution of MBs among stroke subtypes. It is especially noteworthy that the diffuse group was more frequent in pICH, ATBI, and LI compared with other types of stroke. Such distinct differences might be explained by a close relationship between small-vessel diseases (SVDs) and MBs.[3,8,10,18] SVDs (particularly those of an ischemic nature, such as leukoaraiosis, WMH, periventricular hyperintensities, and lacunae), were more frequent in patients with stroke subtypes closely related to hypertension, including pICH, LI, and ATBI.[8,26-28] Thus, the higher prevalence of diffuse MBs in patients with a stroke subtype closely related to hypertension might reflect target organ damage of the whole brain due to chronic hypertension. Other findings